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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/756,978 | 01/09/2001 | Eugene Roussel | 210582.0001/1US | 6809 |

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| EXAMINER | |
|---|---|
| YU, MISOOK | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1642 | |

DATE MAILED: 07/19/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Advisory Action | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/756,978 | ROUSSEL, EUGENE | |
| | Examiner | Art Unit | |
| | MISOOK YU, Ph.D. | 1642 | |

***--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --***

THE REPLY FILED 03 June 2004 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☐ The period for reply expires _____months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☒ A Notice of Appeal was filed on *26 May 2004*. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2. ☐ The proposed amendment(s) will not be entered because:

   (a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);

   (b) ☐ they raise the issue of new matter (see Note below);

   (c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

   (d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____.

3. ☒ Applicant's reply has overcome the following rejection(s): none.

4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5. ☒ The a)☒ affidavit, b)☒ exhibit, or c)☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: *See Continuation Sheet*.

6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7. ☒ For purposes of Appeal, the proposed amendment(s) a)☐ will not be entered or b)☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:

   Claim(s) allowed: _____.

   Claim(s) objected to: _____.

   Claim(s) rejected: *1-66, 81, 83*.

   Claim(s) withdrawn from consideration: _____.

8. ☐ The drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.

9. ☐ Note the attached Information Disclosure Statement(s)( PTO-1449) Paper No(s). _____.

10. ☒ Other: *Exhibit A*

LARRY R. HELMS, PH.D
PRIMARY EXAMINER

Misook Yu, 7/15/04

Continuation of 5. does NOT place the application in condition for allowance because:

Applicant argues that the role of protease is to release one or more antigens from tumor cells, does not require to kill tumor cells on its own, and insists that the Examiner ceases reading into these claims a limitation that is not recited therein. These arguments have been fully considered but found unpersuasive because the Office has not read a limitation not recited in the claims. The preamble of the base claim clearly says that the claimed method is to induce tumor cell death and the dependent claim 4 and 5 clearly recite proteases, thus the Office does not read a limitation not recited in the claims.

Applicant also argues that Wald reference (1998) discloses that a rectally administered protease in combination of other conventional treatment decreased metastasis of an implanted melanoma xenograft in mice, and similarly Kuriyama reference (2001) discloses that no increase in tumor metastasis could be detected when trypsin is locally injected into glioblastoma xenografts. This and other arguments have been fully considered but found unpersuasive because the instantly claimed invention is not drawn to method of inducing apoptosis of glioblastoma xenografts, but drawn to method of inducing tumor cell death in a human patient. Kuriyama reference (2001) is about protease treatment in combination with gene therapy for glioblastoma in mice and Wald reference is about protease treatment in combination with cancer. Thus, applicant is arguing limitation not present claims. In other words, instant claims exclude method involving xenografts. Further, Gura (Exhibit A, 1997, Science, vol. 278, pages 1040-1041) teaches at page 1041, middle column that "the results of xenograft screening turned out to be not much better than those obtained with the original models, mainly because the xenograft tumors don't behave like naturally occurring tumors in humans-they don't spread to other tissues, for example. Thus, drugs tested in the xenografts appeared effective but worked poorly in humans". Thus, one of skill in the art would have reason to doubt the efficacy of the protease, based on glioblastoma xenografts, for inducing tumor cell death in a human patient".

As for 103 rejection, applicant argues that Lee reference is in vitro experiment and anti-Fas antibody is inoperative as an embodiment of antigen-releasing agent in the claimed invention because leukocytes also express Fas antigens, thereby giving anti-Fas antibody would kill leukocytes that have to be attracted to the tumor site in a human patient. These arguments have been fully considered but found unpersuasive. Since the anti-Fas antibody is locally administered into tumor directly, the locally administered anti-Fas antibody in Lee reference (note "peritumorally" at page 232, right column, lines 5) would not kill leukocytes in circulation. Leukocytes expressing Fas antigen do not appear to be the applicant's discovery. The art appears to know well before the effective filing date of the instant application that leukocytes express anti-Fas. Thus, one of ordinary skill would be more motivated to administer anti-Fas antibody directly (locally) into tumor instead of administering it systematically so that cancer-fighting leukocytes are killed by systematic administration of anti-Fas antibody such as intravenous injection.